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Automated Meta-Analysis of Breast Cancer Radiotherapy Complication Risks Using GPT-4 and LLaMA 3.1 Large Language Models

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ADMINISTRATIVE INFORMATION

Support - This study was supported financially, in part, by grants from the National Science and Technology Council (NSTC) of the Executive Yuan of the Republic of China (113-2221-E-992-011-MY2).

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 June 2025 and was last updated on 18 June 2025.

INTRODUCTION

Review question / Objective Population (P): Patients with breast cancer (any subtype); Intervention (I): Photon radiotherapy (e.g., IMRT, VMAT, 3D-CRT); Comparison (C): Proton radiotherapy (e.g., PSPT, IMPT); Outcome (O): Radiation-related complications (e.g., skin toxicity, pneumonitis, cardiac toxicity); Study design (S): Original clinical studies, including retrospective and prospective studies (excluding reviews, case reports, and commentaries).

Rationale This systematic review and meta-analysis aims to evaluate the differences in complication risks between photon and proton radiotherapy in breast cancer patients by applying large language models (LLMs) to automate the review process. The study explores the feasibility and accuracy of using GPT-4o and LLaMA 3.1 models to perform literature screening, data extraction, forest plot generation, and quality assessment.

Condition being studied Breast cancer is the most common malignancy in women worldwide. Postoperative radiotherapy is a standard adjuvant treatment for reducing the risk of local recurrence and improving overall survival. However, radiation-induced complications such as skin toxicity, pneumonitis, and cardiotoxicity can significantly affect patients' quality of life. While photon therapy remains widely used, proton therapy offers more precise dose distribution, potentially reducing radiation exposure to normal tissues. This review aims to compare the complication risks between photon and proton radiotherapy in breast cancer patients.

METHODS

Search strategy The literature search was conducted using a structured strategy based on the PICOS framework. The following electronic databases were searched: PubMed, Web of Science, and Scopus, with the latest search

performed in April 2025. No language restrictions were applied.

Participant or population This review will include patients diagnosed with breast cancer of any subtype, regardless of stage or histological classification.

Intervention The intervention of interest is photon radiotherapy, including techniques such as Intensity-Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), and Three-Dimensional Conformal Radiation Therapy (3D-CRT).

Comparator The comparator is proton radiotherapy, including techniques such as Passive Scattered Proton Therapy (PSPT) and Intensity-Modulated Proton Therapy (IMPT).

Study designs to be included This review will include original clinical studies, including prospective or retrospective cohort studies, non-randomized controlled trials.

Eligibility criteria In addition to the PICOS criteria, the following eligibility conditions will be applied:
Inclusion:
Full-text articles available.
Studies must provide explicit numerical data on complications (either counts or percentages with sample size) for both photon and proton therapy groups.
Exclusion:
Studies that report only dose distributions or dosimetric modeling without clinical outcome data.
Studies that do not distinguish complication outcomes between photon and proton groups.
Articles using secondary data without reporting original patient results (e.g., meta-analyses, reviews).
Non-English full-texts (if not retrievable in complete form despite search).

Information sources Electronic databases to be searched include: PubMed, Web of Science, and Scopus. The search will cover all studies published up to April 2025, with no language restrictions during search. Additional sources such as reference lists of included articles will be manually screened to identify potential eligible studies.

Main outcome(s) The primary outcome is the incidence of radiation-related complications in breast cancer patients who received either photon or proton radiotherapy. Risk Ratio (RR) and Odds Ratio (OR) will be used as the main effect size measures to compare complication risks between the two treatment groups.

Quality assessment / Risk of bias analysis The quality of included studies will be assessed using the Newcastle–Ottawa Scale (NOS), which is suitable for cohort and case-control studies. Each study will be evaluated across three domains:
Selection (maximum 4 points)
Comparability (maximum 2 points)
Outcome (maximum 3 points)Studies scoring ≥6 points will be considered high quality.

Strategy of data synthesis Data from included studies will be synthesized through meta-analysis using both fixed-effect and random-effects models. For each study, the number of patients with complications and total sample size in the photon and proton groups will be extracted. Risk Ratios (RR) and Odds Ratios (OR) with 95% confidence intervals (CIs) will be calculated. Forest plots will be generated to visualize individual and pooled effect sizes. Heterogeneity will be assessed using I^2 statistics and Cochran's Q test. Publication bias will be evaluated through funnel plots and Egger's regression test. All analyses will be performed using Python or RevMan software.

Subgroup analysis Subgroup analysis will be conducted based on the severity grade of skin toxicity, specifically comparing the risk ratios between Grade ≥1 and Grade ≥2 radiation-induced skin reactions. This aims to assess whether the severity of skin complications differs between photon and proton radiotherapy.

Sensitivity analysis No sensitivity analysis is planned in this review.

Country(ies) involved Republic of China (Taiwan).

Keywords Large Language Models; GPT-4o; LLaMA3.1; Meta-analysis; Breast cancer; Proton therapy.

Contributions of each author
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